

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

APPROVAL LETTER

NDA 20-903

June 3, 1998

Schering-Plough Research Institute
Attention: Joseph F. Lamendola, Ph.D.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 3, 1997 new drug application, NDA 20-903 submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Intron® A/Rebetol™ (Interferon alfa-2b, recombinant/Ribavirin), 3 million IU injectable/200mg capsule, and amended to provide for the name Rebetrone™ Combination Therapy.

We acknowledge receipt of your amendments dated:

| | | |
|-----------------------|-------------------|----------------|
| September 26, 1997 | February 17, 1998 | April 24, 1998 |
| January 12, 1998 | March 3, 1998 | May 8, 1998 |
| January 15, 1998 (2) | March 11, 1998 | May 12, 1998 |
| January 20, 1998 | March 17, 1998 | May 29, 1998 |
| February 16, 1998 (2) | March 26, 1998 | |

This new drug application provides for the use of ribavirin capsules in combination with interferon alpha 2-b, recombinant for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the use as recommended in the enclosed marked-up draft labeling submitted on June 2, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the June 2, 1998 draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-903. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated May 13, 1998 and May 29, 1998. These commitments, along with any completion dates agreed upon, are listed below. Further, we acknowledge that the commitments for development of a patient information sheet and package to accommodate dose modification, as stated in your May 13, 1998 submission, have already been completed.

1. **Carcinogenicity Studies** - During 1998, Schering Corporation will initiate three dose-finding studies; one in Sprague-Dawley rats, one in CD-1 mice and one in the C57BL/6 TACF BR-(KO) p53 N5 Wild Type mouse strain (background strain for the p53 KO mouse). Schering will submit the data of these studies with a proposal and justification for which bioassays and doses will be used for review by the Division and the CAC.
2. **Food Effect** - Schering Corporation will assess the feasibility of potential clinical trial designs that might produce relevant data to address the question of whether dosing Rebetol with or without food in the clinical setting markedly changes the safety or efficacy profile.
3. **Voluntary Pregnancy Registry** - Schering Corporation agrees to establish a voluntary pregnancy registry that will be in operation at launch.
4. **Additional Patient Populations** - Schering Corporation agrees to conduct additional studies to evaluate the safety and efficacy in the treatment of naïve patients, pediatric patients, HIV/HCV co-infected patients, transplant patients and patients with cirrhosis.
5. **Long Term Follow-up** - All four pivotal phase 3 studies (2 in relapse and 2 in naïve patients) include a separate long-term follow-up protocol for patients to be followed for five years. Schering commits to working with the investigators to encourage all patients regardless of response, to participate in these studies. This data will be submitted for review, as available.
6. **Validation of Surrogate Markers** - Schering agrees to analyze the clinical database in hepatitis to assess the relationship between virologic and histologic response with different treatments (Intron A monotherapy and in combination with Rebetol, and pegylated Intron A with and without ribavirin) as those programs progress and data become available.

7. Investigation of the safety and efficacy of lower doses of ribavirin in combination with interferon - The results from study C96-114, which is currently ongoing, will be submitted to the NDA upon completion.

Validation of the regulatory methods has not been completed. At present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirement for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Terrie L. Crescenzi, R.Ph., Regulatory Management Officer at (301) 827-2335.

Sincerely yours,

Heidi M Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research